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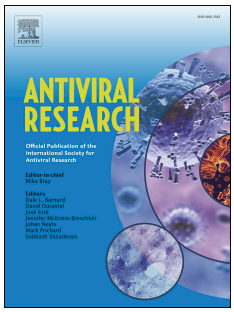

Pharmacokinetics and tissue diffusion of ganciclovir in mice and rats

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Pharmacokinetics and tissue diffusion of ganciclovir in mice and rats

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Abstract:

Background:

Congenital cytomegalovirus (CMV) infection is the leading infectious cause of birth defects, mental retardation and non-genetic sensorineural hearing loss. Murine models have been developed in order to understand the pathophysiological mechanisms underlying these lesions. These models are being proposed for the validation of therapeutic protocols for clinical use. The aim of this preclinical study was to assess the pharmacokinetics of the reference antiviral molecule, ganciclovir, in order to optimize these protocols and confirm the diffusion of the molecule to the appropriate target zones.

Methods:

Transplacental and intracochlear diffusion of ganciclovir was evaluated in mice and rats. Pharmacokinetics was assessed in adult mice and pups after 5 consecutive days of intraperitoneal injection of ganciclovir. The occurrence of hematological side effects of ganciclovir was evaluated in the different blood cell lineages.

Results:

In adult rats, the intracochlear diffusion of ganciclovir was shown to achieve the same concentration as in blood. In gestating mice, transplacental diffusion was observed, with a fetal-to-maternal blood ratio of 0.5. In newborn mice, the plasma concentration profile of ganciclovir showed a peak at 2 hours followed by a gradual decrease. In adult mice, the concentration peaked at 1 hour, but became undetectable by 2 hours after injection.

Counts of white blood cells, red blood cells and platelets decreased significantly in ganciclovir-treated newborn mice.

Conclusion:

Our data provide evidence for the intracochlear diffusion of the molecule, which may be relevant for the treatment of sensorineural hearing loss in congenitally-infected children.

Introduction:

Congenital cytomegalovirus (CMV) infection is the leading infectious cause of congenital malformations, mental retardation and deafness in newborns, and is found in 1% of live births. Ten to 20% of infected children develop sequelae, of which sensorineural hearing loss is the most common. Congenital CMV infection is the second cause of congenital deafness, after genetic factors (Benoist et al., 2008; Dollard et al., 2007; Picone et al., 2009).

The reference treatment for symptomatic neonatal infection is currently the antiviral ganciclovir [9 - (1, 3-dihydroxy-2-propoxymethyl) guanine or DPHG], a nucleoside that inhibits the in vitro replication of human herpes viruses (Herpes simplex type 1 and type 2, CMV) and adenovirus serotypes 1, 2, 4, 6, 8, 10, 19, 22 and 28. Ganciclovir is phosphorylated to its active form, ganciclovir triphosphate, preferentially in infected cells, with concentrations being 10 times lower in uninfected cells (Adler et al., 2007; Barbi et al., 2006). Ganciclovir triphosphate exerts its antiviral activity by inhibiting viral DNA synthesis through two mechanisms: competitive inhibition of viral DNA polymerases and direct incorporation into viral DNA, leading to the blockage of elongation (Donnelly and Brown, 2004). However, at therapeutic doses, as a side effect, it inhibits progenitor cell proliferation in the bone marrow in direct proportion to its blood concentrations.

Murine and guinea pig models in which pups develop sensorineural hearing loss have been developed in order to better understand the cochlear and cerebral lesions associated with congenital CMV infection in human newborns(Bravo et al., 2003; Donnelly and Brown, 2004; Juanjuan et al., 2011; Schachtele et al., 2011). However, in order to study the safety and effectiveness of antiviral therapies in limiting these lesions, it is necessary to carry out preclinical studies of the pharmacokinetics of these molecules in mouse pups to determine the optimal dose and study potential side effects.

The purpose of this study was therefore to assess the pharmacokinetics and transplacental passage of ganciclovir in non-infected pups and adult mice. Several doses of ganciclovir have been used in mice (ranging from 15 to 80 mg/kg/day). Here, we chose to use a supraclinical dose of 100 mg/kg/day (Duan et al., 1998; Lenzo et al., 2001; Qiao et al., 2011; Shimamura et al., 2013), knowing that drug metabolism is higher and its elimination faster in small animals than in humans (Martignoni et al., 2006); in comparison, the therapeutic dose in children is 32 mg/kg/day. We focused especially on the diffusion of ganciclovir into the cochlea, as well as its side effects on blood cell lines.

Materials and methods

1. Animals

Non-inbred Oncins France 1 (OF1) mice (12 adults, 160 newborn mice, and 1 pregnant female) and 2 albino rats non-immunized for MCMV were used (Charles River, France) (Table 1). Once in our animal facility, housing and maintenance of animals were carried out according to the recommendations of the French National Institute of Health and Medical

Research. (Accreditation No. A751901). The experimental protocol was approved by the Institut Claude Bernard Ethics Committee in Paris.

2. Pharmacokinetics in adult mice

Injection protocol:

Ganciclovir (Roche, Bale) was diluted in 5% glucose serum (Glucose Monohydrate 5%, Lavoisier, Paris) to a concentration of 5 mg/ml and administered intraperitoneally in adult mice (40 grams each) at a dose of 50 mg/kg twice a day. A total of five injections was administered.

Samples:

Twelve **adult mice** were evaluated.

Blood samples were collected by intracardiac puncture in adults under isoflurane anesthesia before sacrifice, at 1 hour (T1), 2 hours (T2), 3 hours (T3), 4 hours (T4), 6 hours (T6) and 12 hours (T12) after administration of the 5th and last injection of ganciclovir.

For each time point, blood samples from 2 adult mice were collected.

Samples were immediately centrifuged for 10 minutes at 4°C at 10,000 rpm; plasma was collected and stored at -20°C until analysis.

3. Pharmacokinetics in newborn mice

Injection protocol:

Ganciclovir at a concentration of 5 mg/ml was administered intraperitoneally in newborn mice at a dose of 50 mg/kg twice a day,. Five injections were administered in total.

The mean weight of newborn mice was 2 g on postnatal day 1 (P1), and 4 g at P3.

Samples:

One hundred and sixty **newborn mice** received 5 injections of ganciclovir intraperitoneally at 12-hour intervals starting on P1.

Blood samples were taken from mice immediately before sacrifice, at seven time points: 1 hour (T1), 2 hours (T2), 3 hours (T3), 4 hours (T4), 6 hours (T6), 8 hours (T8) and 12 hours (T12) after the last injection of ganciclovir.

Given the small volume of blood in neonatal mice, for each time point, blood samples from 3 mice were collected and pooled.

4. Maternal-fetal transfer of ganciclovir

A pregnant OF1 mouse was selected at E18, 3 days prior to delivery. After being weighed, the mouse received a daily dose of 2.5 mg (100 mg/kg/day) of ganciclovir intraperitoneally, divided into 2 injections 12 hours apart. Four hours after the 6^{th} injection, the female mouse gave birth. The mother and 4 newborn pups were then sacrificed and the following samples were collected: blood and kidneys of the mother, blood and brains of the pups.

5. Intracochlear passage of ganciclovir in adult rats

After being weighed, two adult rats underwent peritoneal injections. The first rat received 50 mg/kg of ganciclovir twice a day (i.e. 100 mg/kg/day), for a total of 3 days or 6 injections. The second rat was used as a negative control and received intraperitoneal injections of glucose solution. After the 6^{th} injection, the two rats were sacrificed; blood and perilymphatic fluids were collected immediately after dissection of the cochlea through a transcanal approach under microscopic visualization according to the following procedure. After retrieval of the eardrum, the promontory was gently fractured and removed, exposing the membranous labyrinth. The perilymphatic fluid was removed using a micropipette. The same procedure was performed on the contralateral cochlea, and the two samples were pooled together in order to obtain the critical volume of 10 µL per rat, the minimum volume required for HPLC measurements. Ganciclovir concentrations were measured in the plasma and in the perilymphatic fluid in the negative control rat and the ganciclovir-treated rat.

6. Ganciclovir assay

Concentrations of ganciclovir were determined by HPLC with UV detection at 254 nm. Perchloric acid (35% in water) was added to each sample for a final concentration of 3,5% and centrifuged to remove protein. Then 20 µL of cleared supernatant was injected into a a 150 4.6mm Hypersil ODS 3 mm column (Lindsay, 1987). An HPLC system (Thermo Separation Products, Waltham, USA) consisting of a P200 pump, an AS3000 autosampler and a UV2000 spectrophotometer was used. The mobile phase consisted of 0.02 M potassium dihydrogen phosphate adjusted to pH 3.2 with phosphoric acid, with a flow rate of 1.0 mg/ml. The calibration curve for ganciclovir was linear over the range of 0.5–25 mg/mL. The lower detection limit was 0.25 mg/mL. K1 and K2 for ganciclovir standards were 2.5 for 2 mg/L and 15.11 for 15 mg/L respectively.

7. Hematological study

Blood cell counts were performed in newborn mice, in particular in order to investigate the presence of neutropenia. Eight newborn mice were treated using the same ganciclovir protocol described previously, and eight control newborn mice received saline.

At the time of sacrifice, blood was collected by intracardiac puncture in an EDTA tube and manually agitated to prevent coagulation. The tubes were then promptly sent to the pediatric biological hematology department. Cell counts were assessed manually on slides and automatically (Procan-PE-6800) when the sample volume permitted.

8. Data analysis

Results are expressed as means ± standard deviation. Student t-test and Mann-Whitney-Wilcoxon analysis were performed using GraphPad Prism version 5.0 for MacOS (GraphPad Software, San Diego, CA; www.graphpad.com). Significance was considered when $p < 0.05$.

Results

1. Animals and outcome

The mortality rate secondary to injections of ganciclovir in neonatal pups was 13.8% (n= 22/160): hematomas at the site of injection (n=10) and low weight (n=12) were observed in dead pups.

2. Pharmacological study of ganciclovir

a. Ganciclovir concentrations and pharmacokinetic profile in adult and neonatal mice

In adult mice, ganciclovir reached a plasma concentration of 0.81 µg/mL at T1, and was not detectable thereafter (Figure 1).

In neonatal mice, the peak ganciclovir plasma concentration was 6.6 µg/mL at T2; the concentration then progressively decreased and was undetectable by T12 (Figure 2).

b. Bioavailability results

Maternal-fetal transfer of ganciclovir: Blood concentrations of ganciclovir were similar in the mother and pups (6.56 and 5.46 µg/mL respectively). Lower but detectable concentrations were measured in the pups' brains and kidneys (1.75 and 2.20 µg/mL respectively).

Intracochlear transfer: In treated rats, ganciclovir was detectable in the perilymphatic fluid (1.8 µg/mL) at approximately half the plasma concentration (3.83 µg/mL). All samples were negative in control rats. .

3. Hematological study

The effect of ganciclovir was assessed on red blood cells (hemoglobin) (Figure 3A), neutrophils (Figure 3B) and platelets (Figure 3C). A significant decrease in hemoglobin, neutrophils and platelet was observed in ganciclovir-treated mice compared to controls ($p < 0.05$).

Discussion:

Ganciclovir is the reference drug for the management of symptomatic CMV infection, including in newborns (Kimberlin et al., 2008). However there are no preclinical studies available to improve its administration, in particular to reduce side effects (temporary low white blood count). We aimed to provide information on the disposition and potential

hematological side effects of ganciclovir in a murine model using supra-therapeutic doses administered by the peritoneal route (Donnelly and Brown, 2004; Kimberlin et al., 2008; Lackner et al., 2009).

Our results show that the pharmacokinetics of ganciclovir differ between adult and newborn mice, with a higher peak plasma concentration and slower elimination in newborn animals. In addition, ganciclovir crosses the placental barrier when injected into gestating mice, with plasma concentrations in newborn pups close to maternal concentrations. More importantly, ganciclovir can diffuse into the brain and kidneys of pups, as well as the inner ear. The latter point was demonstrated in adult rats, as the volume of perilymphatic fluid in mice, especially neonates, is too low to allow the accurate measurement of ganciclovir. These data are relevant for human patients, and support the use of ganciclovir to treat hearing loss and neurological handicap related to congenital CMV infection, where active viral replication persists for several years (Sugiura et al., 2003; Teissier et al., 2011; Teissier et al., 2014).

In human adults, ganciclovir disposition is characterized by linear pharmacokinetics over the range of 1.6 to 5 mg/kg (Cymevene, 2011). It is eliminated by glomerular filtration and active tubular secretion. In adults with normal renal clearance, the plasma half-life of ganciclovir is 2.9 +/- 1.3h. However, pharmacokinetic studies are limited in immunodeficient patients with severe CMV infections, who receive multiple drugs. In HIV+/CMV+ patients receiving 5 mg/kg ganciclovir intravenously, the peak plasma concentration is 9.03 +/- 1.42 μg/mL one hour after administration and the C_{min} is 0.56 μg/mL 11 hours after injection. Diffusion into the cerebrospinal fluid has been measured in 2 patients, and attains concentrations between 0.5 and 0.68 μg/mL, corresponding to 24-67% of the concomitant plasma concentrations (Cymevene, 2011).

In children, pharmacokinetics has been studied in patients aged 9 months to 12 years with normal renal function. The C_{max} after twice daily injections of 5 mg/kg is 7.59 +/- 3.21 μg/mL on day 1 (Cymevene, 2011).

In adult mice, pharmacokinetics showed a peak ganciclovir concentration at T1 or earlier but concentrations became undetectable at T2, while in pups, the peak concentration occurred at 2 hours post-injection with a progressive decrease thereafter. Although procedures for drug administration and sample collection were standardized, the variability of plasma concentrations was probably increased by technical difficulties such as the small sample volume obtained for each pup, requiring pooling. Variability could also have been due to changes in weight, making precise dosage adjustment difficult.

The therapeutic effect of ganciclovir is dose-dependent. The selection of the dose tested in the present study (100 mg/kg/24h) was guided by doses used in previously published work (Duan et al., 1998; Lenzo et al., 2001; Qiao et al., 2011; Shimamura et al., 2013). Although the weight-adjusted dose was higher than therapeutic doses in humans (32 mg/kg/24h), a lower dose would probably have led to insufficient plasma concentrations, considering the rapid elimination of the molecule. Furthermore, systemic concentrations in adult and newborn mice were found to be lower than plasma concentrations in humans.

However, this high dose may have increased side effects (Forster et al., 2010; Shimamura et al., 2013). In humans, neutropenia is the most frequent toxic side effect associated with ganciclovir and valganciclovir therapy(Marshall and Koch, 2009). To our knowledge, there is no study evaluating the side effects of ganciclovir or correlating them to dosage in mice. In our study, at the high dose tested, the toxicity of ganciclovir was observed in all blood cell lines and may have participated in the mortality rate observed in this series. An in vitro study has demonstrated that ganciclovir exhibits duration-dependent toxicity to hematopoietic-

derived cells in vitro (Janoly-Dumenil et al., 2009). However, mortality was also influenced by the occurrence of hematomas at the site of injection and the low birth weight of the offspring. These data should be considered when analyzing survival rates in infected animals after ganciclovir treatment. Because hematological toxicity is dose-related, the optimization of the dosing schedule is required to increase its therapeutic index (Janoly-Dumenil et al., 2012).

Conclusion:

Ganciclovir is the antiviral drug of choice currently used in patients with congenital CMV infection, yet few if any preclinical studies on its pharmacokinetics exist in the literature. Our study has allowed the pharmacokinetics of high-dose ganciclovir to be characterized in a murine model. In addition, we have confirmed its transplacental passage in gestating mice as well as its diffusion into the brain and the perilymphatic space of the inner ear. However, our study has also demonstrated the hematotoxicity of high-dose ganciclovir in different blood cell populations in mice. The current challenge in the management of congenital CMV infection is to identify effective therapeutic molecules with a satisfactory benefit/side effect balance. Other drugs devoid of myelotoxicity, such as maribarvir, are currently under evaluation for the prevention of congenital CMV infection in mouse models, but their clinical efficacy has not yet been proven. Additional preclinical animal studies using various therapeutic doses are therefore necessary to obtain a complete picture of the pharmacokinetics and toxicity profiles of these molecules, and design effective treatments to prevent the long-term sequelae of congenital CMV infection in children.

Acknowledgements

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TABLE AND FIGURE LEGENDS

Figure 1: Plasma concentrations of ganciclovir versus time in adult mice following intraperitoneal administration at 50mg/kg twice daily. Staring at H2, the ganciclovir

concentration passes under detection threshold. The blue line represents the mean concentration for each sampling time and bars the standard deviation.

Figure 2: Plasma concentrations of ganciclovir versus time in newborn mice following intraperitoneal administration at 50mg/kg twice daily. The blue line represents the mean concentration for each sampling time and bars the standard deviation.

Figure 3: Average hemoglobin (A) (g/dl), neutrophils (B) (number/ml) and platelet counts (C) (number/ ml) in the treated and control groups. Error bars account for the standard deviation.

Figure 1

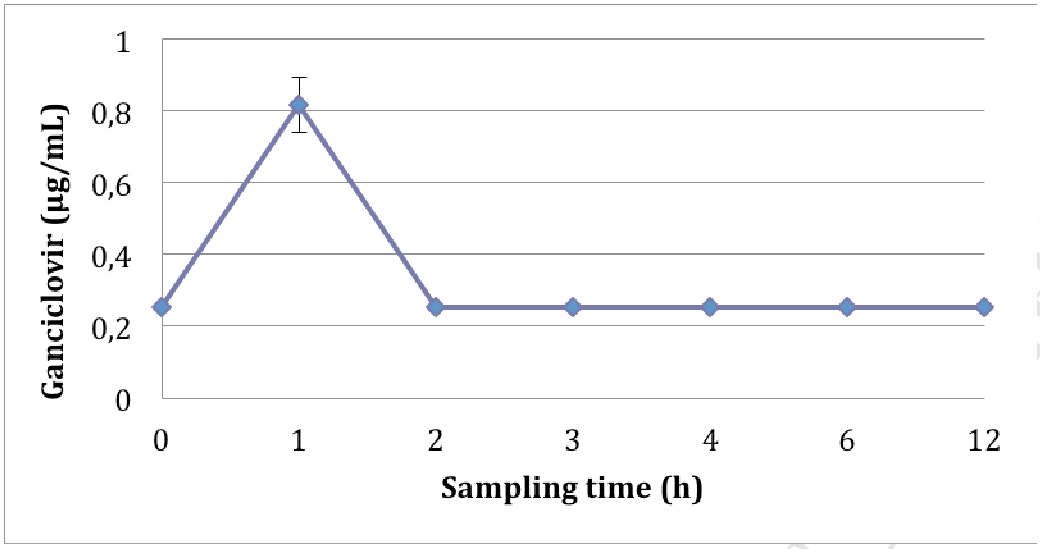


Figure 2

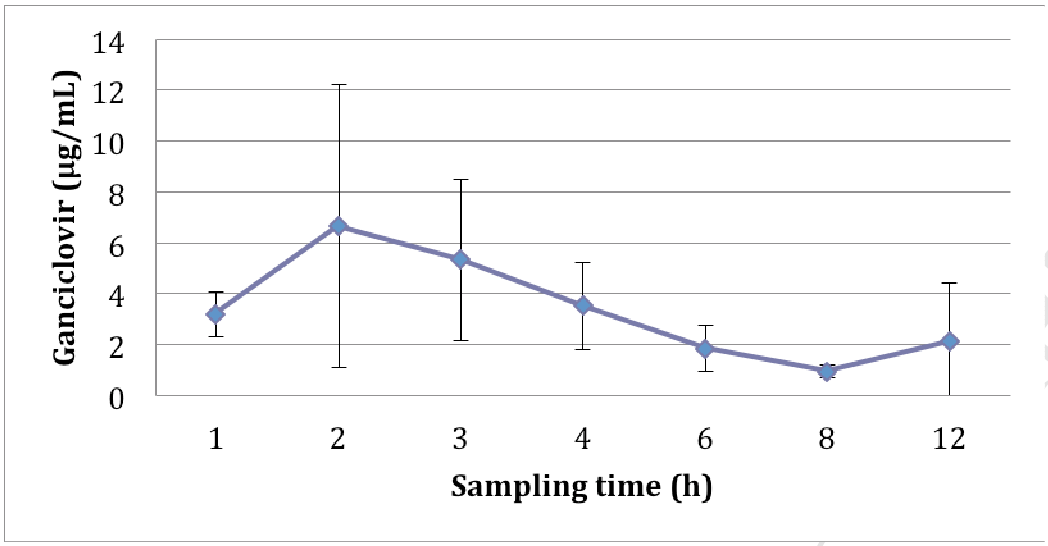
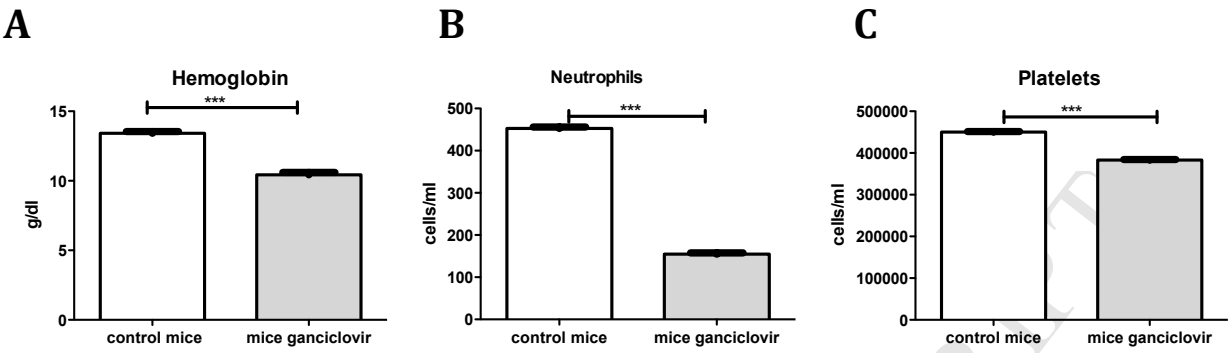


Figure 3



Pharmacokinetics and tissue diffusion of ganciclovir in mice and rats

- Transplacental and intracochlear diffusion of gangiclovir in mice and rats: first-time proof of inner ear diffusion
- Pharmacokinetics in adult mice and pups: differences important to consider
- Ganciclovir toxicity on different cell lineages in mice